A CONTRIBUTION TO THE KNOWLEDGE OF THE PATHOLOGY OF FRAGMENTATION AND SEGMENTATION, AND FIBROSIS OF THE MYOCARDIUM.

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PLATES XXI AND XXII.

In order to make clear the following description of the minute changes taking place in the heart-muscle cell, it will be well first to describe briefly the appearances met with in normal cardiac muscle. In a previous paper* I have given a detailed description of these, together with an account of the histogenesis of the cardiac muscle cell.

HISTOLOGY OF THE MUSCLE OF THE NORMAL HEART.

The normal adult heart muscle of the human subject is made up of irregular rhomboidal cells, which are usually considerably branched. Each cell consists of darkly staining columns, which run longitudinally and are separated by unstained substance. These columns are commonly spoken of as fibril bundles, and correspond with what v. Kölliker has called "Muskelsäulchen." The unstained substance between is generally known as sarcoplasm.

Careful observation and certain methods of special staining reveal a definite relation between these two parts of the cell. The fibril bundles are striated like voluntary muscle, showing a narrow disc called Krause's membrane, and a broader disc or Brücke's line of doubly refractive substance between each two narrow striations. Krause's membrane corresponds with the "Zwischenscheibe" of German writers, and Brücke's line is identical with the "Querscheibe."

* J. B. MacCallum, On the Histology and Histogenesis of the Heart-muscle Cell, *Anatomischer Anzeiger*, 1897, xiii, 609.

In thin sections, especially those stained by Kolossow's method, the Krause's membranes are seen to belong to the sarcoplasm as well as to the fibril bundles (Plate XXI, Fig. 1). The sarcoplasm is divided into distinct discs by membranes which horizontally are continuous with the Krause's membranes of the fibril bundles. There may be more than one of these discs between two adjacent fibril bundles (Plate XXI, Fig. 1, A); and at the centre of the cell the perinuclear sarcoplasm is made up of discs alone.

Seen in transverse section (Plate XXI, Fig. 2) the cell consists of darkly staining masses which are cross-sections of fibril bundles, separated by definite discs of unstained substance, the sarcoplasmic discs. The muscle fibre then contains a continuous network, made up of the fibril bundles, and the membranes bounding the sarcoplasmic discs. The points of junction of these membranes with the fibril bundles are at the narrow striations or Krause's membranes of the fibril bundles.

The relation of these parts is made clear by their histogenesis. The earliest stage in the development of the heart-muscle cell shows an irregular network in the protoplasm. This tends to become more regular as shown in Plate XXI, Fig. 3, assuming the form of discs which in transverse sections are seen as clear circular areas. Some of these discs break up into smaller ones, and in the angles between them there is an accumulation or a differentiation of the substance of the network, giving rise to longitudinally disposed masses. The earliest formation of these is around the periphery of the cell as shown in Plate XXI, Fig. 4. They become what in the adult cell are known as fibril bundles, and the discs left in between are the sarcoplasmic discs described. It is thus seen that the network, composed partly of the fibril bundles, is derived directly from the primitive network of the embryonic cell. It is further a very noticeable fact that the formation of fibril bundles takes place first at the peripheral part of the cell, so that those fibril bundles which are formed latest are nearest the centrally placed nucleus.

In the state of extension the muscle fibre differs very markedly from the condition described above. It often happens, especially in cases

of fragmentation of the myocardium, that two cells, separated only by a cement line, are in the state of contraction and extension respectively. The contracted fibre is much broader than the other, and, on following it to the cement line, the edges suddenly narrow down when the next cell is reached, as shown in Plate XXI, Fig. 5. It is evident that the narrow cell is the extended one, and the histological characters of it indicate that it has undergone a very decided change. The most noticeable differences are the following:—In the extended fibre the lateral edges are distinctly concave, as compared with the slightly convex boundaries of the contracted cell. The fibril-bundles are much closer together in the extended fibre, and seem to occupy relatively more space than in the contracted condition. As a consequence of this the sarcoplasm is much less in evidence. Within themselves also the fibril bundles show marked changes. The distance between each two narrow striations or Krause's membranes is very much greater than in contracted muscle. In this space there is a darkly staining mass which has on each side, between it and the respective Krause's membranes, a clear space. This dark body corresponds in position with the secondary striation, or Brücke's line. It is, however, very different in form from this structure in contracted muscle. It is generally somewhat narrower, and considerably longer. Whereas in contracted fibres its transverse diameter is two or three times as great as its length,in extended muscle it is either equally great in both axes, or even greater in the long axis. As represented in Plate XXI, Fig. 5, B, the most conspicuous striation in contracted muscle is Krause's membrane; while in the extended condition (Fig. 5, A) Brücke's line becomes very distinct, and the narrow striations are hardly to be seen.

METHODS AND MATERIAL.

For the following study of some of the pathological conditions met with in heart muscle, only human tissues were used. These were obtained in part fresh from autopsies made in the Johns Hopkins Hospital, and in part from already preserved specimens. With regard to some of the tissues used in the study of fragmentation and

segmentation, I am greatly indebted to Dr. Hektoen of Chicago, who, at the request of Dr. Flexner, sent a number of exquisite specimens to the laboratory.

All the tissues that were obtained fresh were treated by Kolossow's osmic acid method,* and also by the ordinary methods. The other tissues were hardened in Zenker's fluid, alcohol or Müller's fluid. Sections were cut in both celloidin and paraffin.

The tissues treated by Kolossow's method were studied without further staining. The others after being cut were submitted to a treatment somewhat similar to that described in Kolossow's method. The sections were placed in 1 per cent osmic acid for 2—5 minutes until they were thoroughly impregnated. They were then transferred to Kolossow's reducing fluid (tannic and pyrogallic acids) until the precipitation was complete. If the stain is not intense enough, this process may be repeated, care being taken, however, that all the reducing fluid is washed out with water before the sections are again put into osmic acid. The sections may be dehydrated and mounted in the ordinary way. This mode of staining is not by any means recommended in place of Kolossow's original method, for it gives much less distinct pictures. It is, however, convenient, in that tissues hardened by any of the ordinary methods can be used, while in the original method only fresh tissues can be employed. A nuclear stain may be obtained in connection with this, by treating the sections subsequently with safranin.

Specimens stained in hæmatoxylin and eosin, safranin, and van Gieson's fluid were also studied.

FRAGMENTATION AND SEGMENTATION OF THE MYOCARDIUM.

Renaut and Landouzy† in 1877 were the first to describe a dissociation of the muscle cells of the heart. They believed that it was due to nutritive disturbances, which acted in such a way that the cement substance between the cells was softened. They called the condition "segmentation."

*A. Kolossow, Ueber eine neue Methode der Bearbeitung der Gewebe mit Osmiumsäure, *Zeitschr. f. wissenschaftl. Mikroskopie*, 1892, ix, 38.

† Renaut, Note sur les altérations du myocarde accompagnant l'inertie cardiaque, *Compt. rend. Société de Biologie*, July, 1877.

Renaut* in 1890 contributed another article in which he considers the condition as a definite disease; and attributes the separation of the cells to a solution of the cement substance.

Von Recklinghausen † believes that breaking may take place in the cell-body as well as in the cement line, and that it is due to irregularities in contraction, rather than to a solution of the cement substance.

Israel‡ observed that there is a separation of the muscle bundles, suggesting that the change is brought about by mechanical influences.

Browicz§ believes that the dissociation of the muscle cells occurs before death, and may give rise to insufficiency or even stoppage of the heart.

According to Oestreich|| breaking takes place mainly in the body of the cell, although it may occur in the cement line. The condition cannot be brought about by decomposition, and all the evidence points to its being an ante-mortem process. Oestreich cites instances of its presence in sudden deaths, death under chloroform, etc. It may occur in almost any disease.

Bard¶ believes that the breaking occurs after death, in muscle which is abnormally fragile.

It is thus believed by some, particularly Browicz, Renaut, Tedeschi, Israel, and Durand** that there is some chemical substance formed which acts on the cement leading to its solution.

By others, especially v. Recklinghausen, Oestreich, and Bard, the condition is thought to be brought about mechanically.

Since these works a paper has appeared by L. Hektoen,†† in which the subject is carefully worked over. Hektoen divides the process definitely into segmentation and fragmentation. The former term is used when breaking on the cement line is meant, while "fragmentation" indicates

* Renaut, *Gaz. méd. de Paris*, 1890, 7. s., vii, 109; 123.

† Von Recklinghausen, *Verhandlungen des X Intern. Congress., Berlin* (1890), ii, Abth. 3, p. 67.

‡ Israel, Zur Entstehung der Fragmentatio myocardii, Virchow's *Archiv*, 1893, cxxxiii, 551.

§ Browicz, Ueber die Bedeutung der Veränderungen der Kittsubstanz der Muskelzellbalken des Herzmuskels, Virchow's *Archiv*, 1893, cxxxiv, 1.

|| Oestreich, Die Fragmentatio myocardii, Virchow's *Archiv*, 1894, cxxxv, 79.

¶ Bard, De la signification anatomique et clinique des diverses lésions du myocardè, *Congrés Français de Médecine*, Paris, 1895, p. 806.

** Durand, Étude anatomique sur le segment cellulaire contractile et le tissue connectif du muscle cardiaque. Thèse, Lyon, 1879.

†† L. Hektoen, Segmentation and Fragmentation of the Myocardium, *American Journal of Medical Sciences*, 1897, cxiv, 555.

breaking on the body of the cell. The two conditions, he thinks, are due to a "disproportion between the vigor and order of muscular contraction and muscular cohesion." According to him fragmentation is possibly, if not probably, due to mechanical agencies; while segmentation cannot be produced in this way.

In a recent paper, Karcher* has reported more especially on experimental fragmentation. He notices the increase in pigment, the swelling of the nuclei, and the changes in the cement substance. His findings confirm the earlier views that the condition is most commonly found in the papillary muscles, less frequently in the left ventricle, and only occasionally in the right ventricle. According to Karcher the causes may be separated into two classes:

1. Fragmentation as the result of sudden injuries or acute processes.
2. Fragmentation following chronic diseases when there is a disturbance of the nutrition of the heart.

Experimentally Karcher obtained fragmentation by cutting the cervical cord and stimulating the peripheral cut end; also by cutting the vagus in the cervical region, and subsequently giving strychnine. He concludes that fragmentation of the myocardium is caused chiefly by disturbances in the nutrition of the heart, especially when associated with a sudden rise in blood pressure.

Histology of the heart muscle in fragmentation and segmentation of the myocardium.

Studied with high powers and with the special methods of staining described, the condition known as fragmentatio myocardii is seen to be a more complex process than a mere breaking of the fibre. In every case where the breaking is at all prominent, there is a peculiar condition of the muscle which consists in an alternating contraction and extension of the fibres. Extension and contraction are not here, as is the case in normal muscle, present in large areas. The cells seem to be affected separately, and one often finds a contracted fibre immediately adjacent to an extended one. In normal muscle the two conditions may be present in the same section, but in such a case all the fibres in one part of the section are contracted and all those in another part are extended. The muscle of fragmentation, however, shows a

* J. Karcher, Ueber die Fragmentation des Herzmuskels, *Deutsches Archiv für klinische Medicin*, 1897, lx, 67.

remarkable distribution of the differently affected fibres. It is very often possible to follow a contracted fibre down to the cement line, and find the cell on the other side of the line suddenly narrowed down to the extended condition, as described above. In such a place the contracted fibre would be separated only by a cement line from the extended one. The same thing is seen even in different parts of the same cell. Bands of contracted and extended tissue alternate with one another, so that in extreme cases the fibre has a mottled appearance. This appearance is certainly pathological, and it is, to say the least, strange to see in the protoplasm of the same cell, two such distinct histological conditions as extension and contraction of muscle fibres.

The breaking which accompanies this condition can be classed under four headings, according to its position and histological character:

1. Breaks occurring in the cement line.
2. Breaks occurring in contracted muscle.
3. Breaks occurring in extended muscle.
4. Breaks occurring as the result of a degenerative process, whose initial stage is an extreme extension of the muscle.

We may then speak of simple fragmentation and degenerative fragmentation.

Histology of simple fragmentation.

This condition is known as segmentation when present in the cement lines, and as fragmentation when the breaks occur in the body of the cell. In segmentation the break takes place in the centre of the line, leaving on either side the "stratum granulosum terminale," to use a term introduced by Przewoski,* which limits the end of the fibre. In the body of the cell the fragmentation differs somewhat according as the muscle is contracted or extended.

(*a*) *Simple fragmentation in contracted muscle.*—The break is irregular and tends to take a stair-like direction (Plate XXI, Fig. 6, A). It is usually a clear break which passes across the breadth of the fibre. It is difficult to determine exactly where the fracture occurs in rela-

* Przewoski, Du mode de réunion des cellules myocardiaques de l'homme adulte, *Archives des sciences biologiques de St. Pétersbourg*, 1893, ii, p. 286.

tion to the fibril bundles and sarcoplasmic discs. It is certain, however, that it is very close to, if not actually in, Krause's membrane. In nearly every instance one can make out this structure at the end of the broken fibril bundle, so placed that it limits the bundle and sarcoplasm at the line of fracture. The line of Brücke is never seen at the broken end of the fibril bundle, and the tendency seems to be for the break to occur always at Krause's membrane. Further, it is always at right angles to the long axis of the fibril bundles, that is to say in the line of Krause's membrane.

(*b*) *Simple fragmentation in extended muscle.*—This condition is much more extensive than the fragmentation just described. There seems to be less resistance against the forces that cause breaking than in contracted muscle. One often sees small breaks on either side of the main one, and there may even be separated fragments of fibril bundles in the line of fracture. As shown in Plate XXI, Fig. 6, B, there is usually an area made up of segments partially or entirely broken off from the fibril bundles. Here also the breaking seems to take place at Krause's membrane, for all the fragments are bounded by this line, as represented in the figure referred to.

Histology of the sarcolytic degeneration of fragmentation.

Thin sections, stained by the methods mentioned above, but particularly by Kolossow's osmic acid method, show definite areas of the muscle fibre from which some of the structural elements seem to have disappeared. These areas stain faintly as compared with the rest of the cell, and present a more or less marked dissociation of the protoplasmic structure. Every gradation can be made out between still solid tissue and areas which are merely a mass of detritus. This condition is shown in Plate XXI, Fig. 7, and will be spoken of as sarcolytic degeneration. When examined more carefully it is seen that those areas which are least changed show a great resemblance to normal extended muscle (Plate XXI, Fig. 8, A). The fibre, or the part affected, becomes somewhat more narrow than the normal tissue, and the minute characters are the same as those mentioned in the description of normal muscle. The first stage in the process, then, is

one which causes the muscle to undergo a change similar to that undergone by normal muscle extension. A gradual transition can be traced from the primary stage to that in which a complete disintegration of the part takes place. In some fibres the rows of Brücke's lines which run across the whole cell, forming the broad striations, are more distant from one another than in extended fibres (Plate XXI, Fig. 8, D). This appearance suggests that a stretching out has taken place which is not due to the simple extension of the cells. In other cells the rows of broad striations become irregular, often drawn down at one side, so that they run obliquely instead of transversely, as shown in Plate XXI, Fig. 8, D. The sarcoplasmic discs are correspondingly irregular and appear only as refractive oval unstained bodies, between the darkly stained masses, as may be seen in some parts of Plate XXI, Fig. 7. In still other fibres the lines of Brücke are so irregularly placed that they cannot be said to form lines at all. They are scattered without order over the degenerating area, and are separated by the sarcoplasmic discs, which now have no definite relation to the remains of the fibril bundles. Some of the discs have broken down, leaving only a granular material. In these areas the cell has become considerably narrowed, and has the appearance of having been very much stretched. There are other places in the fibres where the remains of the fibril bundles can, with difficulty, be made out (Plate XXI, Fig. 9, A). Such areas show simply an irregular mass which stains faintly, and is made up of the granular remains of broken down sarcoplasmic discs, along with an occasional darkly staining fragment from the disintegrated fibril bundles. These places tend to become narrower in the centre and show very irregular edges. It is probable that such a fibre would offer very little resistance to stretching, and what appears to be the last stage in the process of degeneration is often seen in cells which are completely separated by the breaking away or absorption of this narrow central part (Plate XXI, Fig. 9, B).

There thus seems to be a definite process of degeneration, which begins with an extension of the fibre, and ends in its disintegration and separation into fractions. It seems certain that this is a definite

pathological process, presenting several stages in its course. These several stages, although running imperceptibly into one another, may be grouped in the following way:

1. Simple extension of the fibre or part of the fibre, with a lengthening and narrowing of the part.

2. Stretching of the fibre, with the production of irregularities in the rows of striations on the fibril bundles, and changes in the relations of the sarcoplasmic discs to the fibril bundles.

3. A condition of still greater irregularity in the distribution of the fragments of fibril bundles, accompanied by a disappearance of some of them.

4. A disappearance of all the remains of the fibril bundles, leaving only a mass of partly broken-down sarcoplasmic discs.

5. Complete disintegration with a breaking across of the area.

The exact relation between this process and the simple fragmentation in the contracted and extended muscle, and segmentation, is not clear. The various conditions occur in the same muscle, and indeed are nearly always seen in the same section, so that they are obviously closely connected. The simple breaks, especially those in contracted muscle, do not differ materially from fractures which are sometimes caused artificially, for example in the process of sectioning. Histologically they resemble mechanical breaks. In the extended fibre, fragmentation seems to be a more serious condition; for, as described above, the extension occurs in an abnormal way. In normal muscle, one does not find the curious alternation of extended and contracted fibres which is characteristic of this condition. Breaking is more common in extended fibres than in contracted ones, and this would in all probability be the case if both were caused by mechanical forces.

In degenerative fragmentation, on the other hand, the disintegration is apparently a more or less gradual process. When the various states are present together, one does not hesitate to say that the degenerative process is the main lesion. It is a much more extensive change than the others. In a great many of the specimens examined, it was found in every cell in the section, and sometimes in two or more places in the same cell, as shown in Plate XXI, Figs. 7 and 8. It was found

in practically all the cases of fragmentation which were examined, and in the great majority of cases was the most conspicuous lesion, when looked for with high powers. The simple breaks, although sometimes very numerous, seem to be an accessory lesion. With such an extensive process of degeneration as that described, it is certain that much of the muscle would be incapable of carrying out its functions. In such an event, a great deal of extra work and strain would be thrown on the remaining healthy muscle. It is conceivable that this unusual strain might cause such simple breaks as those described. A mechanical explanation like this is supported by the fact that in some cases of fibrous myocarditis, where there is a great deal of muscle thrown out of function, there is seen a simple breaking which resembles in every particular that described. If this be true, the main lesion in fragmentation of the myocardium is a degenerative process, the sarcolytic degeneration described, while the simple breaks in the various locations are mechanical results of the unusual strain thrown on the muscle which remains undegenerated.

If the entire condition of fragmentation is due to unfavorable changes in the nutrition of the cells, it is difficult to imagine that simple breaks could be caused in this way. The alternating contracted and extended fibres might, however, arise from such a condition, although the exact manner in which this could occur is far from clear. Whether the changed nutrition renders certain parts of the fibre incapable of responding to a stimulus; or whether it acts as a stimulus to other parts, leaving the areas between in an extended condition, can only be the subject of hypothesis. The degenerative process, however, must be due to some definite nutritive change, and, if this be so, the most plausible explanation of the simple breaks is a mechanical one.

MUSCLE-CELL DEGENERATION FOUND IN FIBROUS MYOCARDITIS.

Huchard * describes the muscle-cell in fibrous myocarditis as undergoing atrophy, and vesicular or vacuolar transformation. Both conditions are found at the periphery of the islands of muscle which

* H. Huchard, Étude clinique de la cardio-sclérose, *Revue de Médecine*, 1892, xii, 421 et seq.

are formed by the connective tissue growth. In vacuolar transformation the muscle-cells appear empty in the centre so that in transverse section they have a ring-like appearance. In a later stage the cell dissociates. According to Huchard, this vacuolar degeneration is nothing more than an œdema of the cardiac fibre.

According to Bard and Philippe,* the interstitial growth of connective tissue is mainly around the vessels. The muscle fibres undergo a "fragmentary degeneration" and there is an increase in the pigment.

There are generally recognized in fibrous myocarditis two processes, the disappearance of muscle-cells, and the overgrowth of newly formed connective tissue. The latter process, which is, as pointed out by Weigert, probably a secondary one compensating for the loss of the more highly differentiated muscle-cells, consists in a proliferation of connective tissue from the already formed tissue cells. Its main growth seems to be from the connective tissue of the blood-vessels. These areas appear as localized patches, or strands of grayish tissue scattered over the muscle, and may be the seat of calcification.

In a cross section of a fibrous patch one sees islands of muscle fibres, separated by the ingrowing connective tissue. At the periphery of these islands, there are always to be seen cells which appear with the low power to be empty in the centre, as Huchard has said. With a higher magnification, however, these cells show all stages of a very definite process of degeneration.

Appearances met with in cross section.—When compared with the normal tissue, there are some cells in which the central undifferentiated sarcoplasm is somewhat increased. This sarcoplasm, like that in normal cells, consists of small discs. In other cells, a large mass of these discs is present in the centre, surrounded by a very much diminished number of fibril bundles. This mass is usually quite irregular in form but its position is, roughly speaking, in the centre of the cell. One also finds cells where there is only a single row of fibril bundles around the periphery while the rest of the cell is made up entirely of sarcoplasmic discs (Plate XXII, Fig. 10, A). Another appearance often met with is shown in Plate XXII, Fig. 11, where the

* L. Bard and Cl. Philippe, De la myocardite interstitielle chronique, *ibid.*, 1891, xi, 345.

fibril bundles have entirely disappeared, leaving only the discs. The nucleus of a cell at this stage is generally abnormal also. It shows irregularities in outline and an abnormal distribution of the chromatin. In very severe cases, the sarcoplasmic discs themselves tend to break down and become irregular. This was particularly noticed in a heart in which the fibrous areas had become hard and infiltrated with inorganic material. As shown in Plate XXII, Fig. 12, these cells become very small, and are markedly different from the nearly normal cell in the same figure. There are sometimes seen, as shown in Fig. 10, B, large spaces in the cell. These, however, are not constantly present, and are not a part of the process described.

Appearances met with in longitudinal section.—In longitudinal section one finds a structure, which corresponds very closely with that described in cross section. There are cells which present only peripherally disposed fibril bundles, and show a marked increase in the central perinuclear sarcoplasm. Here, also, is particularly well seen the great increase in pigment around the nucleus. As represented in Plate XXII, Fig. 13, other cells are found which show no fibril bundles at all. They are made up entirely of sarcoplasmic discs, with a considerable amount of pigment near the nucleus. The connective tissue, which surrounds these fibres, presses closely upon them, and it is sometimes difficult to say where the muscle stops, and the connective tissue begins. Muscle-cells similar to this but much smaller are also seen (Plate XXII, Fig. 14). The pigment is still abundant, and the cell itself has become spindle-shaped, owing, perhaps, to the pressure of the connective tissue. Its structure is irregular and the discs show signs of breaking up. Finally, one sees, as represented in Plate XXII, Fig. 15, long spindle-shaped spaces in the connective tissue, which contain only the muscle pigment surrounded sometimes by the remains of the cell protoplasm.

It will be seen from the above objective description, that there is in the heart-muscle of fibrous myocarditis a degeneration which runs a definite course. The normal muscle-cell, which is almost entirely filled with fibril bundles, undergoes a change which begins with those most centrally placed. The process of disintegration and solution

goes on from within out, until there is left only a single row of fibril bundles at the periphery of the cell. There are often great irregularities in the disappearance of the fibril bundles, but the general tendency is for them to disappear first in the central part of the cell. At a later stage the peripherally situated fibril bundles become small and disappear, leaving a cell which consists only of sarcoplasmic discs, or what corresponds to the so-called undifferentiated sarcoplasm. Such a cell is usually more or less rhomboidal, but, as the process goes on further, it becomes distinctly spindle-shaped. The size diminishes gradually, until finally there is nothing left but the detritus and a greatly increased amount of pigment.

Such a process as this means little in itself, but if it be considered in connection with the process of histogenesis which has been described, there seems to be a most interesting relation between them. It will be remembered that the cardiac cell appears first as a spindle-shaped structure, containing an irregular network, which tends to become more regular as the development goes on. Seen in cross section, it presents a number of discs which were spoken of as sarcoplasmic discs. Some of these break up into smaller ones, and between them there is an accumulation of the network to form fibril bundles. These fibril bundles form first at the periphery of the cell, and gradually develop toward the centre until the fibre is complete. It will be noticed that the last structures to develop are the fibril bundles at the centre of the cell, and as described above the first structures to degenerate are fibril bundles in this same central position. The degeneration goes from the centre out, while the development has occurred from the periphery in. One very marked stage in the histogenesis is that in which the cells have a single row of fibril bundle around the periphery, and exactly the same stage is observed in the degeneration. Even in the later stages of the degeneration the cells show a marked resemblance to the earlier stages of development. The earliest developmental stage shows a spindle-shaped cell with simple sarcoplasmic discs, while one of the later stages of the degeneration could be described in much the same way. In short, the process of degeneration is approximately a reversal of the developmental process. The first structures to be

formed are the last to degenerate, and the last ones to develop are the first to disappear. Although it has to do with the internal structure of a cell, this process is a striking example of a principle which seems to hold in a number of instances, namely, that the most highly differentiated tissues, or parts of an organ, tend to degenerate first.

In conclusion, I wish to thank Dr. Flexner for the kind interest which he has taken in this study, and for his many helpful suggestions. I am also indebted to Mr. Eggers of this laboratory for the care with which he has prepared photographs for me.

DESCRIPTION OF PLATES XXI AND XXII.

PLATE XXI.

Fig. 1. Longitudinal section of normal adult human heart muscle. *S*, sarcoplasmic discs; *F*, fibril bundles; *K*, Krause's membrane; *A*, the junction of two sarcoplasmic discs.

Fig. 2. Transverse section of normal adult human heart muscle. *S*, sarcoplasmic discs; *C*, central sarcoplasmic mass; *F*, fibril bundles; *A*, junction of two sarcoplasmic discs. The section is through a part of the cell, either above or below the nucleus.

Fig. 3. Transverse section of heart-muscle cells from a pig embryo 10 mm. long. *S*, sarcoplasmic disc.

Fig. 4. Transverse section of heart-muscle cells from a pig embryo 20 mm. long. *F*, fibril bundles; *S*, sarcoplasmic disc.

Fig. 5. Longitudinal section of parts of two cardiac muscle cells separated by a cement line. *A* is extended, *B* contracted muscle.

Fig. 6. Longitudinal section, showing a break in the contracted muscle in *A* and a break in the extended fibre in *B*.

Fig. 7. Microphotograph of longitudinal section of heart muscle showing the degeneration of fragmentation. ×700.

Fig. 8. Longitudinal section of heart muscle showing the earlier stages of degeneration. *A*, extended muscle; *B*, degenerated area; *C*, cement line.

Fig. 9. Longitudinal section of heart muscle, presenting later stages of degeneration. The fibre *B* is broken across as a result of the degeneration.

PLATE XXII.

Fig. 10. Transverse section of degenerating muscle fibres in fibrous myocarditis. *A*, cells in which the peripheral fibril bundles remain. The rest of the cell is made up of sarcoplasmic discs. *B*, a cell which shows large spaces or vacuoles.

Fig. 11. Transverse section of degenerating muscle fibres in fibrous myocarditis. The cells at the edge are normal; the central one has lost all its fibril bundles.

Fig. 12. Transverse section of an area of heart muscle infiltrated with inorganic material in a case of fibrous myocarditis. *A*, connective tissue replaced partly by inorganic material. At the left hand of the figure muscle cells are shown in various stages of degeneration.

Figs. 13, 14 and 15. Longitudinal sections of degenerating fibres in fibrous myocarditis. The fibril bundles have all disappeared. In 14 the cell has become somewhat spindle-shaped, and in 15 only the pigment granules and a suggestion of sarcoplasm remain.

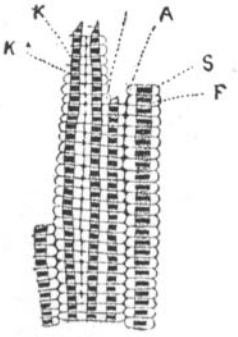

FIG. 1.

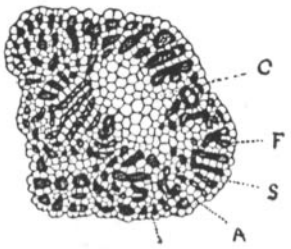

FIG. 2.

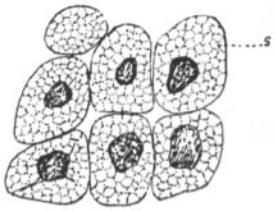

FIG. 3.

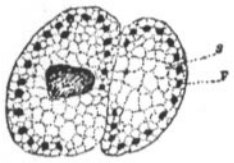

FIG. 4.

FIG. 5.

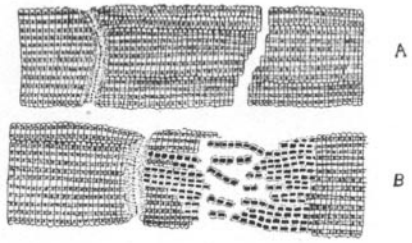

FIG. 6.

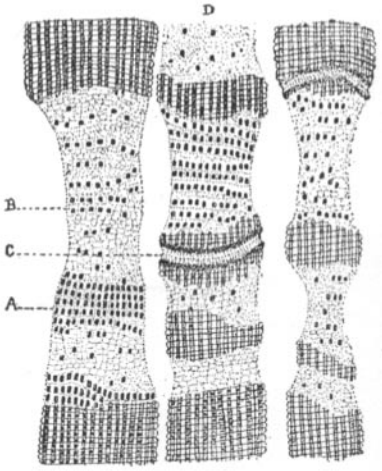

FIG. 8.

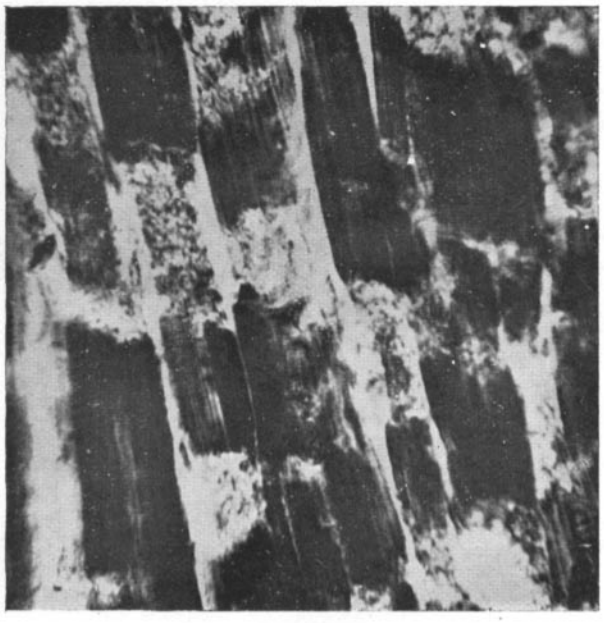

FIG. 7.

FIG. 9.

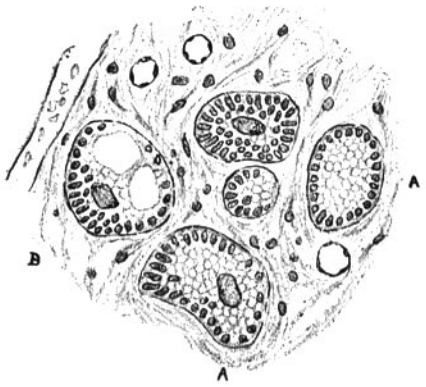

FIG. 10.

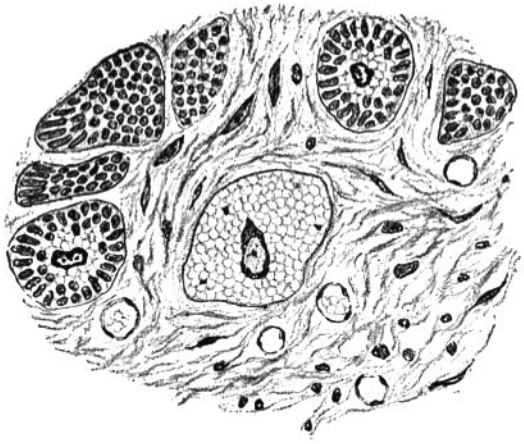

FIG. 11.

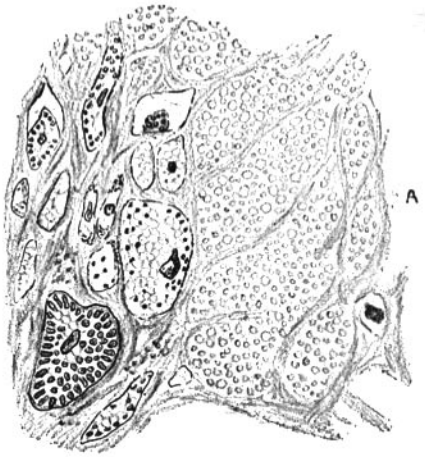

FIG. 12.

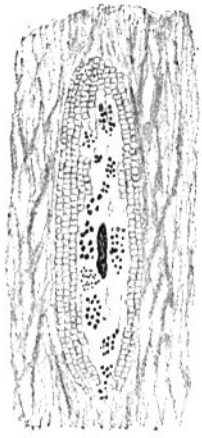

FIG. 13.

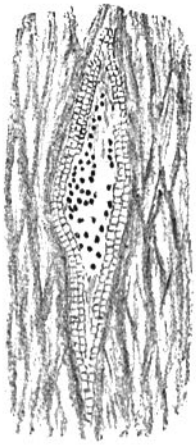

FIG. 14.

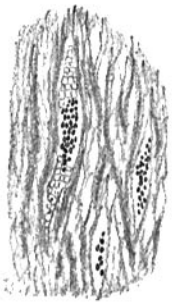

FIG. 15.